Using 3D Shape Matching in AIDD to Design CCR4 Antagonists

Michael Lawless, PhD

Senior Principal Scientist

Please note: this presentation, including questions from the audience, is being recorded and may be made available.

SimulationsPlus MIDD Model Informed Drug Development • 2023

3D Shape Matching in AIDD to Design CCR4 Antagonists

- 3D virtual screening in ADMET Predictor X.5
- AI-driven Drug Design (AIDD) workflow
- CC-chemokine receptor 4 (CCR4) background
- CCR4 receptor antagonists
- Using shape matching in AIDD generate potential CCR4 antagonist

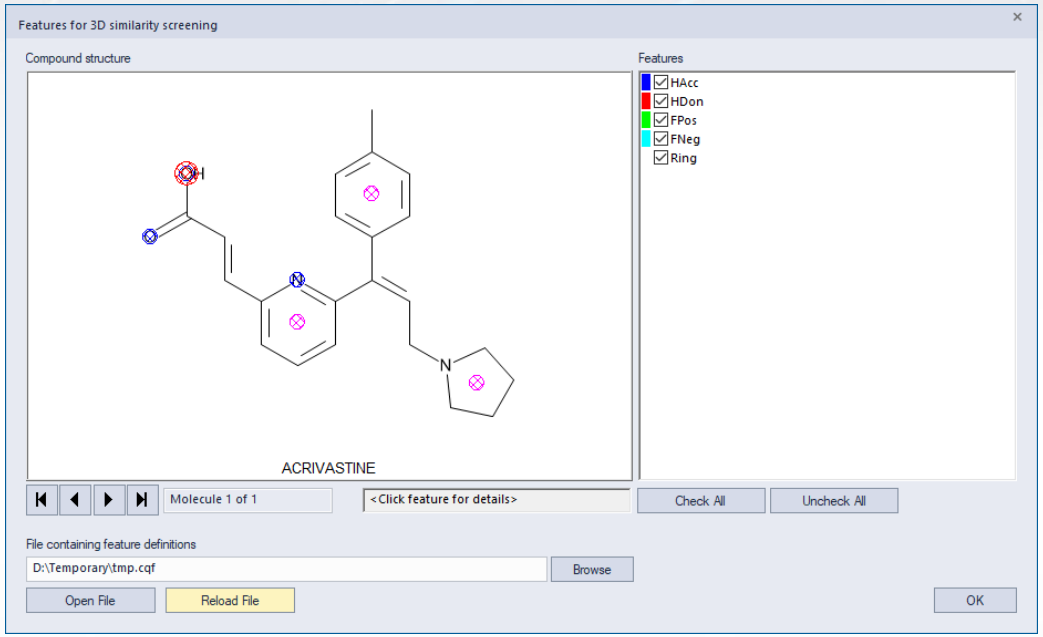
Upcoming features in APX.5

3D Virtual Screening

- Create a 3D conformer database from a set of internally or commercially available compounds
- Perform a similarity screen of the database using one or more reference structures (3D geometry from X-ray or model)
- Similarity screen can run on an NVIDIA GPU for increased performance

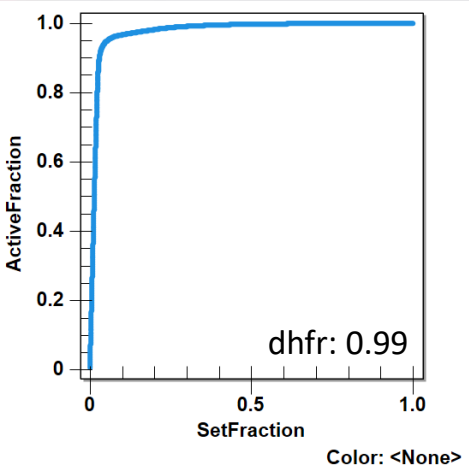
3D Similarity Scores

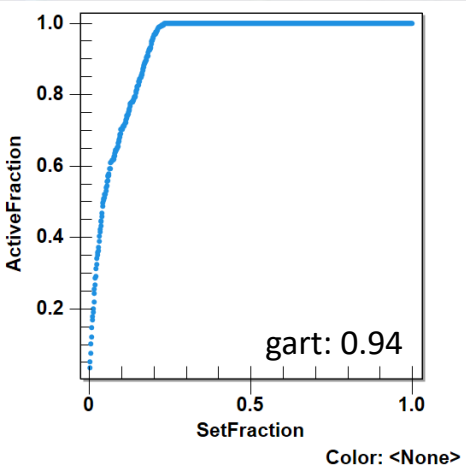
- Similarity scores consist of a shape term based on overlap volume and a feature term based on the alignment of pharmacophore features; users can adjust the relative importance of the two terms
- Overlap volumes are computed using atom-centered gaussian functions; these allow fast computation and are convenient for gradient based optimization
- Features can include hydrogen bond donors and acceptors, positive and negative charges and ring centroids; users can also define their own features

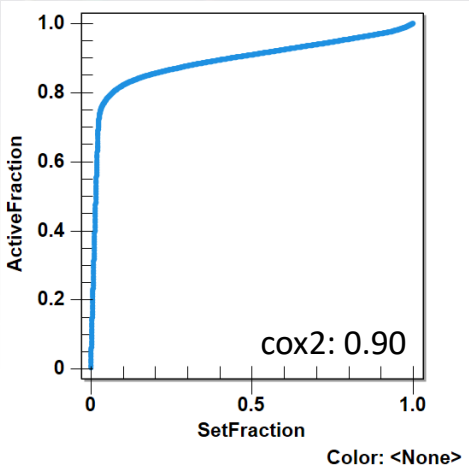


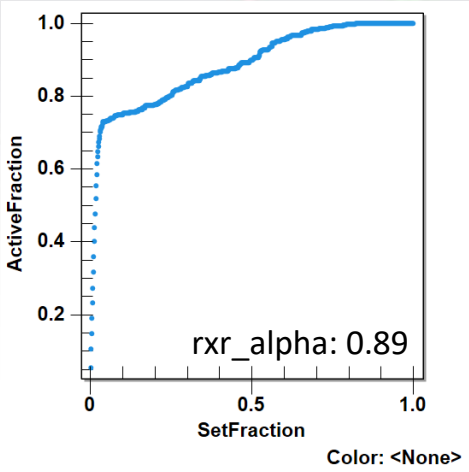
Features can be defined and visualized using a 2D utility

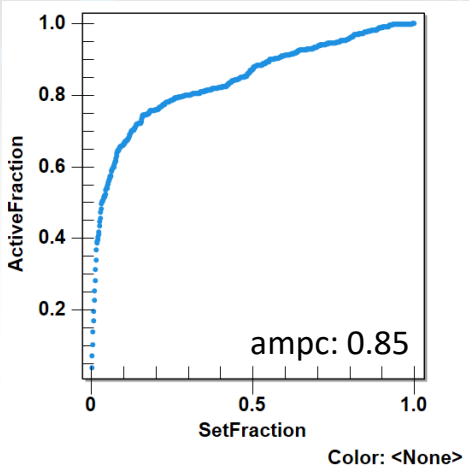
Performance on the DUD set

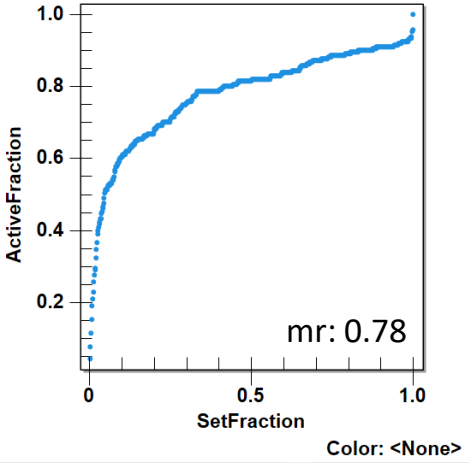


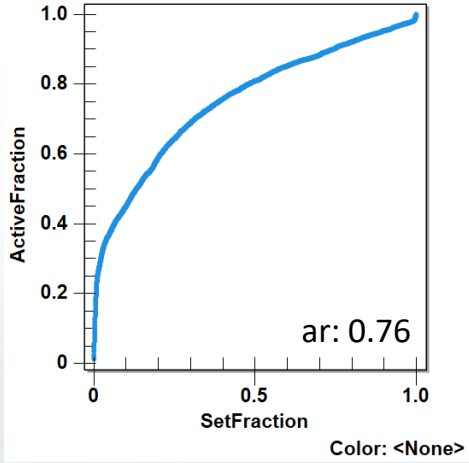


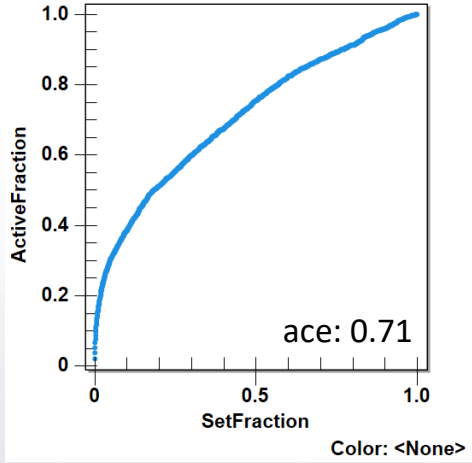


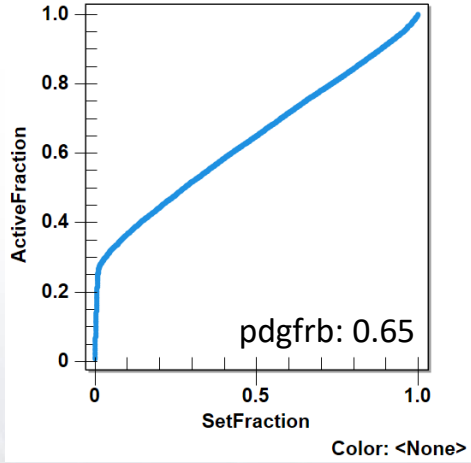


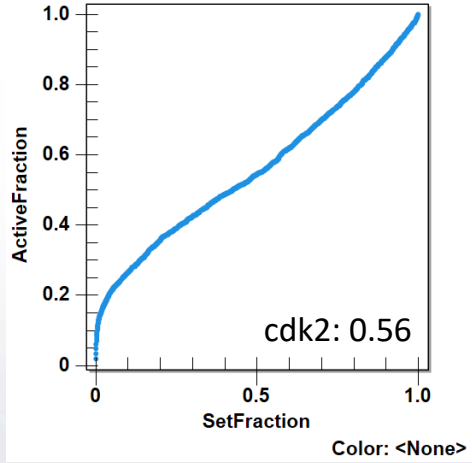








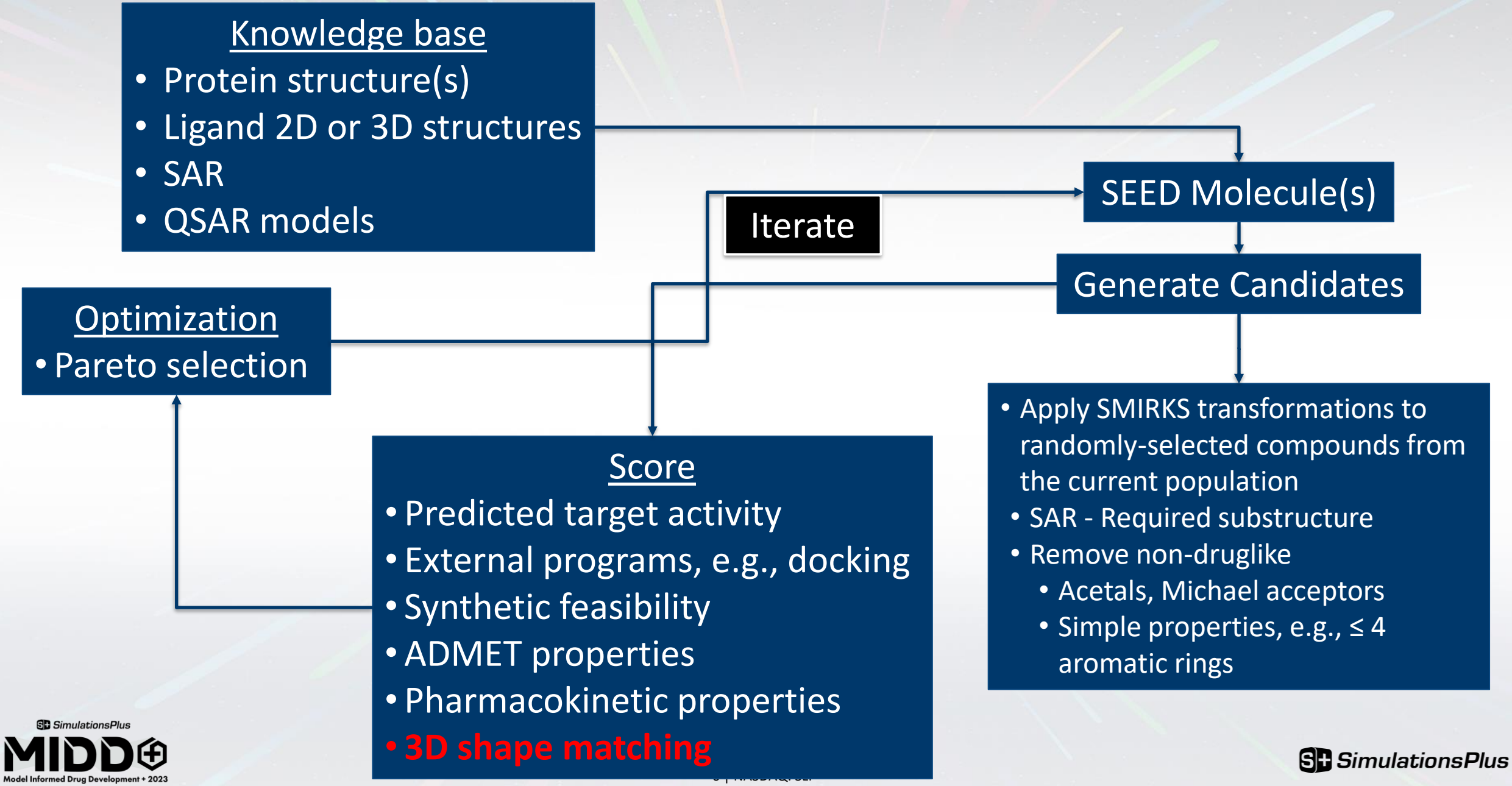




Feature weight = 10

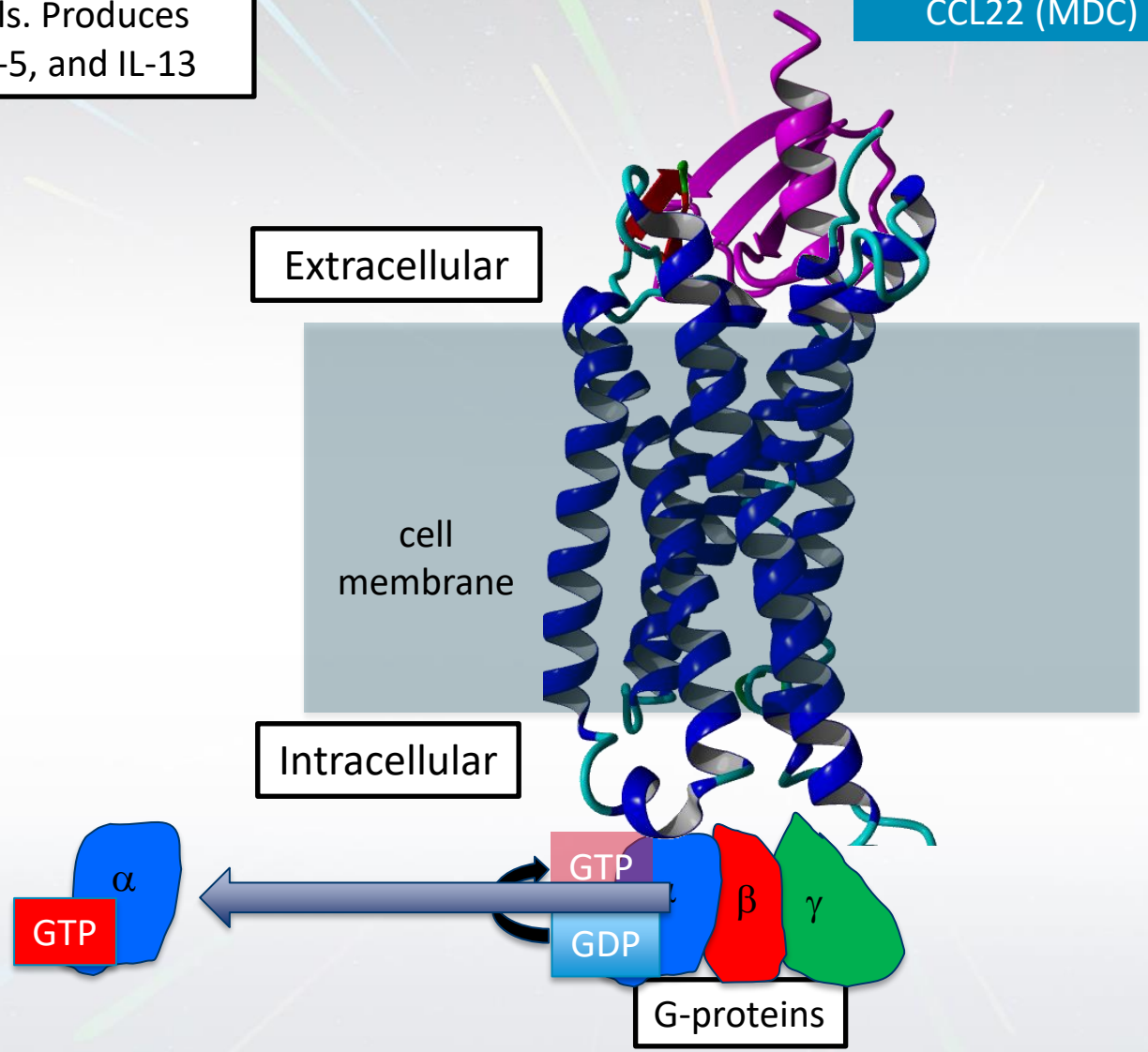
Average AUC = 0.78 (40 targets)

AIDD Workflow



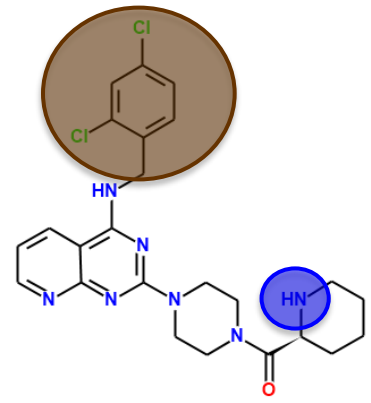
CCR4 is mostly expressed in T helper 2 (Th2) cells. Produces interleukin IL-4, IL-5, and IL-13

CCL17 (TARC) or CCL22 (MDC)



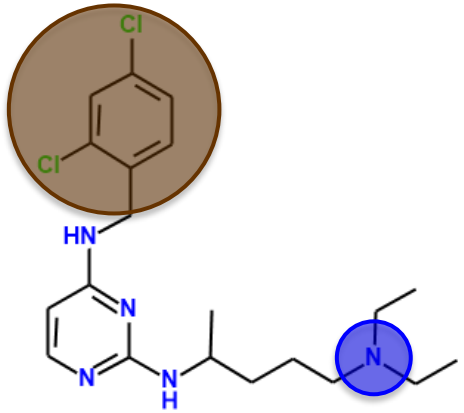
Small molecule CCR4 antagonists have two distinct allosteric binding sites (Slack et al. 2013) and one site is intracellular (Andrews et al. 2008).

CCR4 S1 Allosteric Antagonists



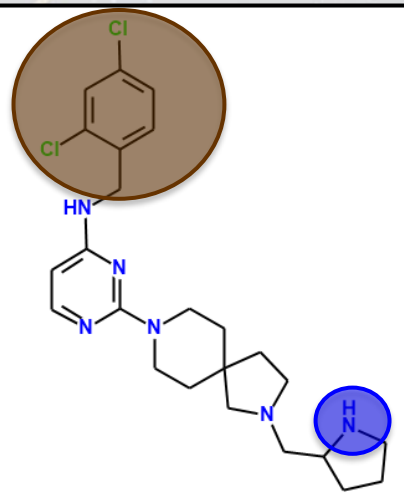
CHEMBL233046

BMS
CCR4 FMAT IC_{50} = 16 nM
(Purandare et al. 2007)



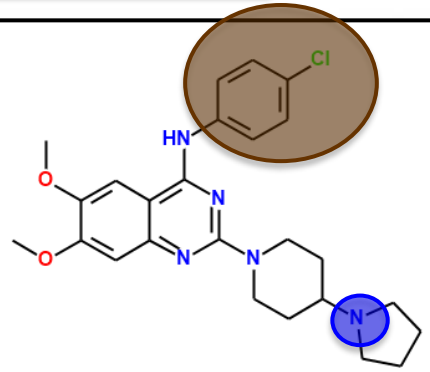
CHEMBL195298

BMS
CCR4 IC_{50} = 270 nM
(Purandare et al. 2005)



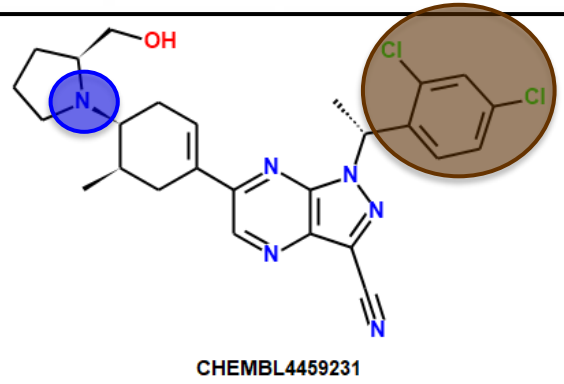
CHEMBL3799266

GSK
CCR4 TARC disp IC_{50} = 1.6 nM
(Shukla et al. 2016)



CHEMBL486840

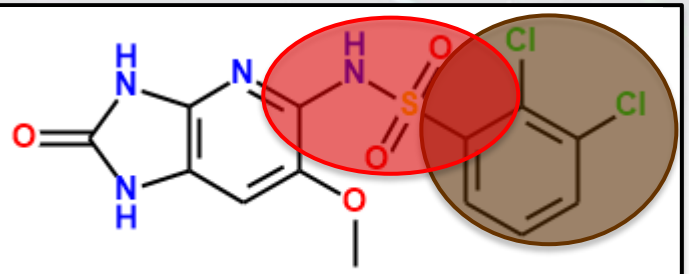
Astellas
CCR4 GTPgS IC_{50} = 24 nM
(Yokoyama et al. 2008)



CHEMBL4459231

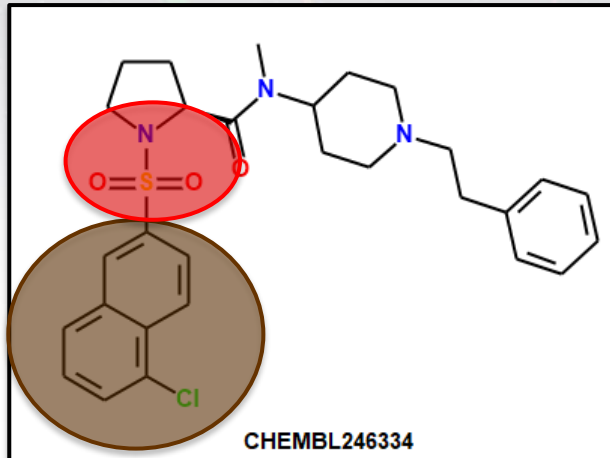
RAPT Therapeutics
CCR4 Ca flux IC_{50} = 40 nM
(Jackson et al. 2019)

CCR4 S2 Allosteric Antagonists



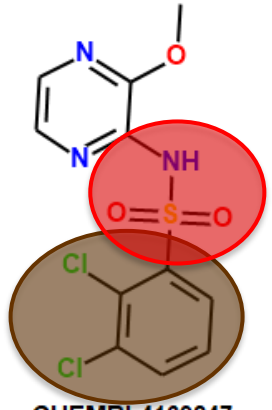
CHEMBL3310839

GSK
CCR4 GTPgS IC_{50} = 25.1 nM
(Miah et al. 2014)



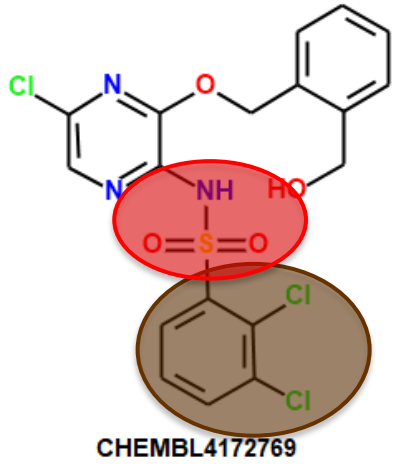
CHEMBL246334

Millennium
CCR4 MDC disp K_i = 100 nM
(Burdi et al. 2007)



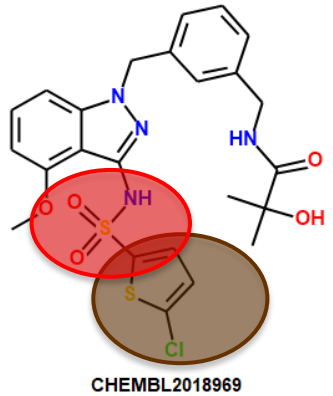
CHEMBL4169247

AstraZeneca
CCR4 FMAT IC_{50} = 15.8 nM
(Kindon et al. 2017)



CHEMBL4172769

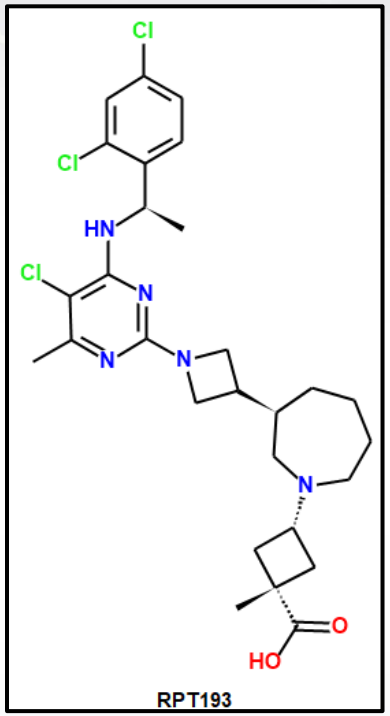
AstraZeneca
CCR4 FMAT IC_{50} = 0.316 nM
(Kindon et al. 2017)



CHEMBL2018969

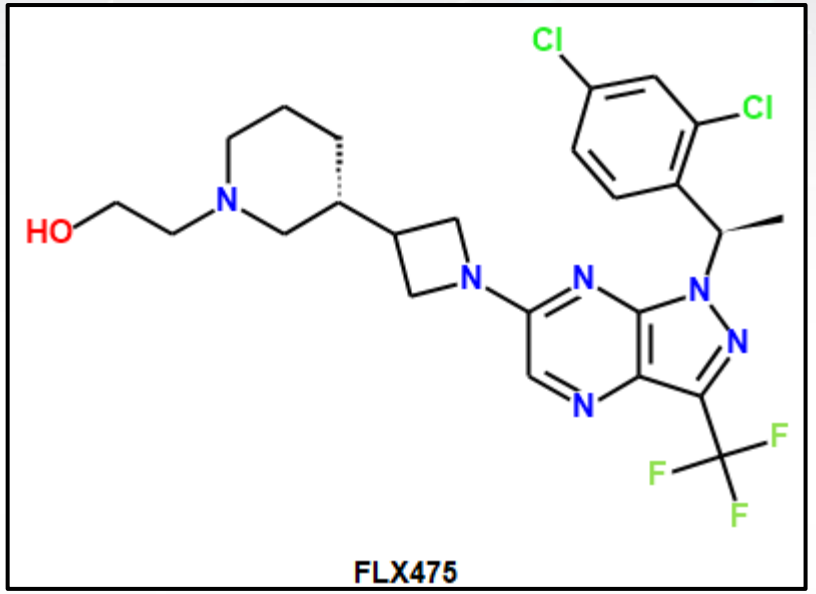
GSK
CCR4 GTPgS IC_{50} = 14.8 nM
(Procopiou et al. 2013)

CCR4 Antagonists Currently in Clinical Trials



RPT193

An orally dosed compound that completed Phase 1b trial for patients with atopic dermatitis (RAPT Therapeutics RPT193).

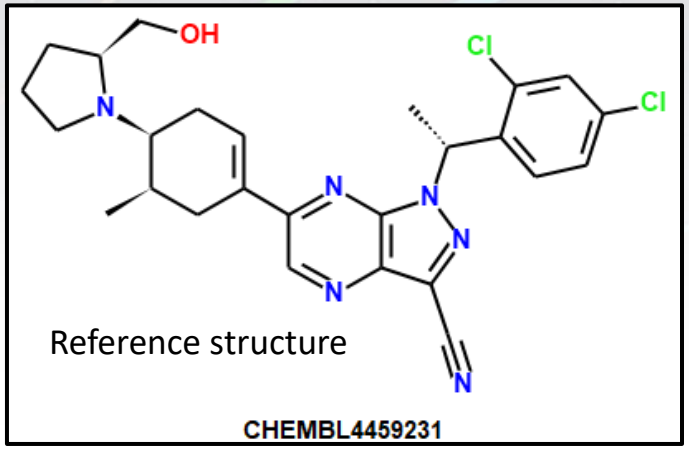


FLX475

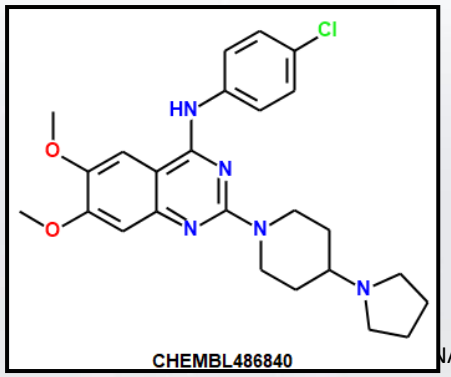
Designed to block T_{reg} (regulatory T cells) migration into tumors. Completed Phase I and enrolling Phase II portion of the study (RAPT Therapeutics FLX475).

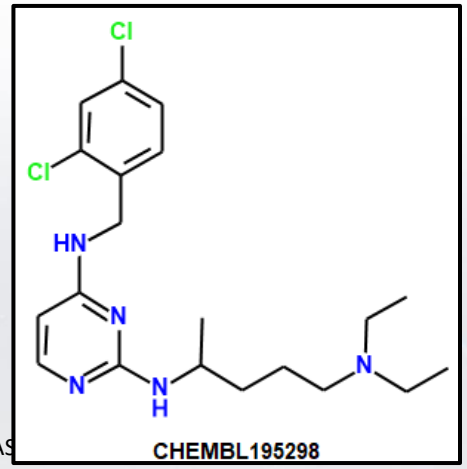
Overlay of Known CCR4 Site 1 Antagonists

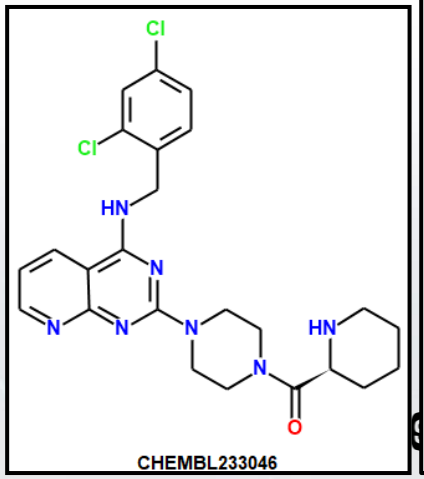
- CHEMBL4459231 reference structure geometry
  - Generate 100 conformations
    - 0.25 minimum RMSD between conformer pairs
    - 10 kcal/mol maximum energy range
    - Minimize lowest energy structure to generate reference geometry
- Candidate database
  - Same as above but store all 101 conformers in database

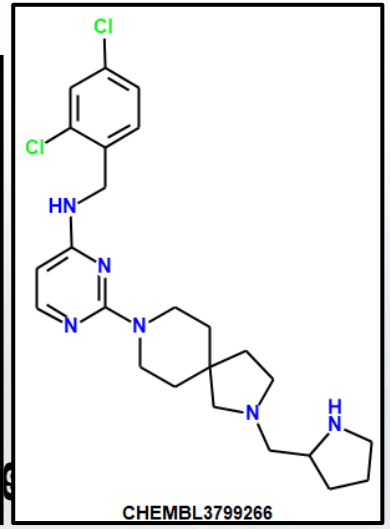


Candidate database compounds

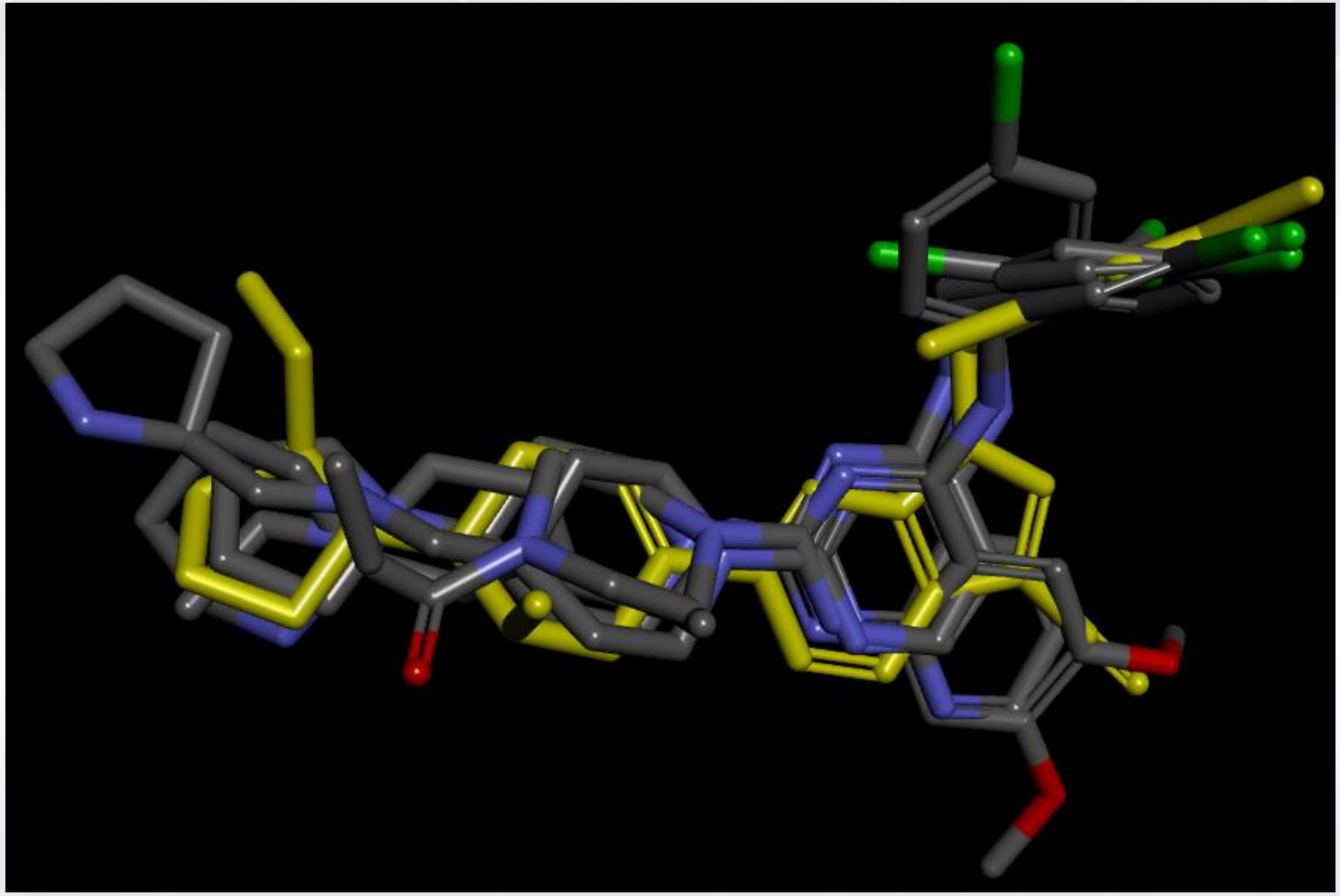








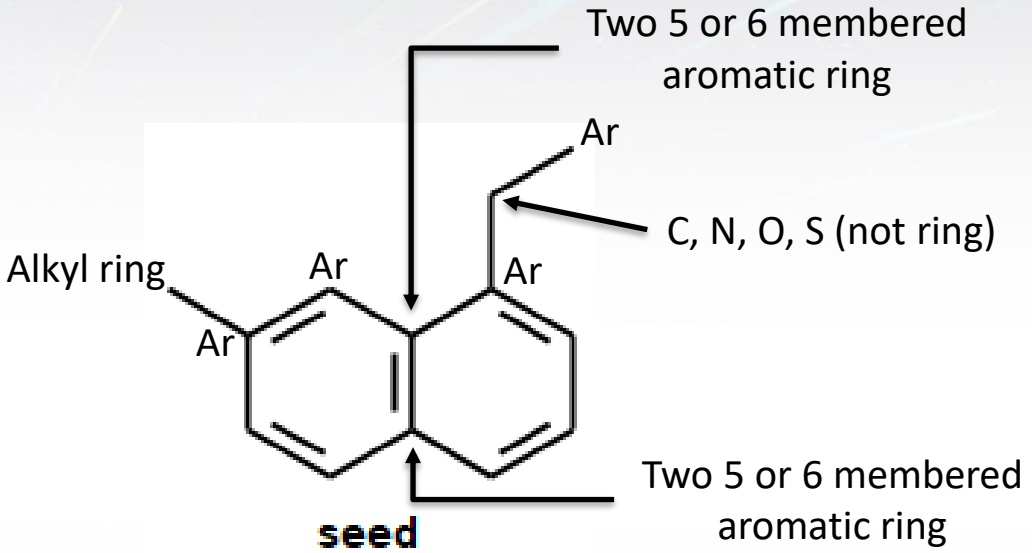
3D Overlay onto RAPT Compound



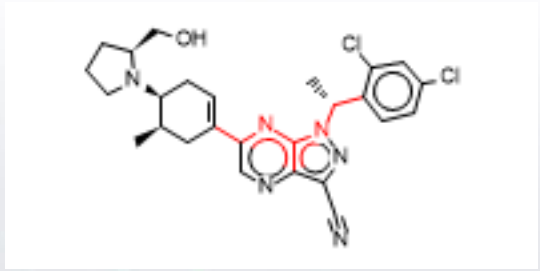
RAPT compound is colored yellow

AIDD shape matches to RAPT pyrazolopyrazine CCR4 antagonists

- Use “simple” seed molecule, 1, 7 disubstituted naphthalene
- Objectives
  - Synthetic difficulty
  - Fraction absorbed
  - Tanimoto from shape matching algorithm
- Scaffold query
  - RAFT molecule pharmacophore ([a;r5,r6]([C,O,N,S;!R][a])[a;r5,r6;R2]([a;r5,r6;R2])[a][a]!@[A;R])
- Druglike filter
  - Limit to 3 Cl, Br, or I (SLQ [Cl,Br,I].[Cl,Br,I].[Cl,Br,I] > 1)
  - Limit to 3 aromatic rings (NPQ ArRing > 3)
  - Limit to 3 CL atoms (SLQ Cl >= 4)
  - Can’t match RAPT molecule
- 10 generations
- 500 candidates per generation
- 1000 initial population



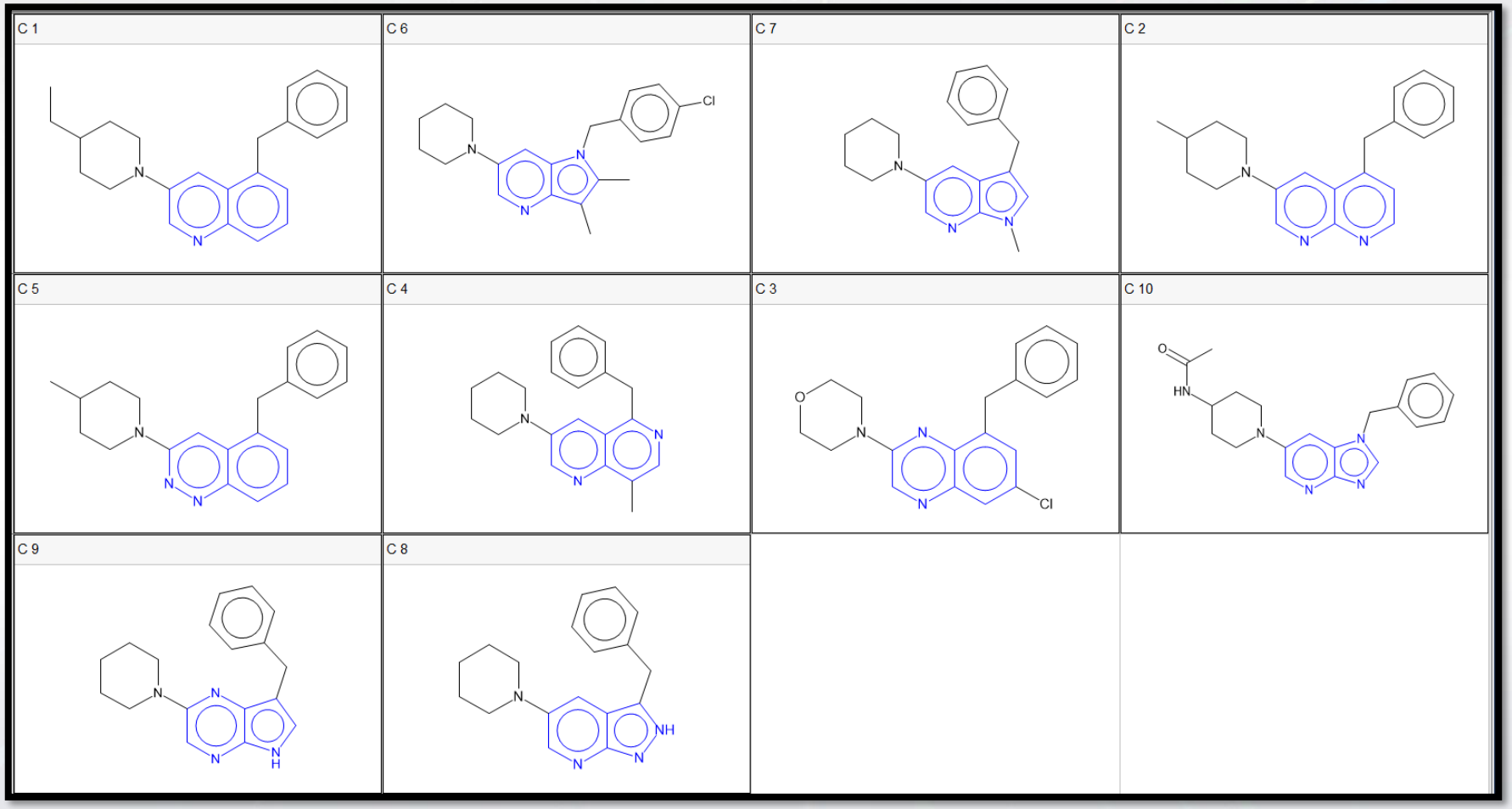
Takes about 15 minutes on a DELL laptop with an Intel(R) Core(TM) i7-10510U CPU @ 1.80GHz with an NVIDIA GPU



Match from scaffold query

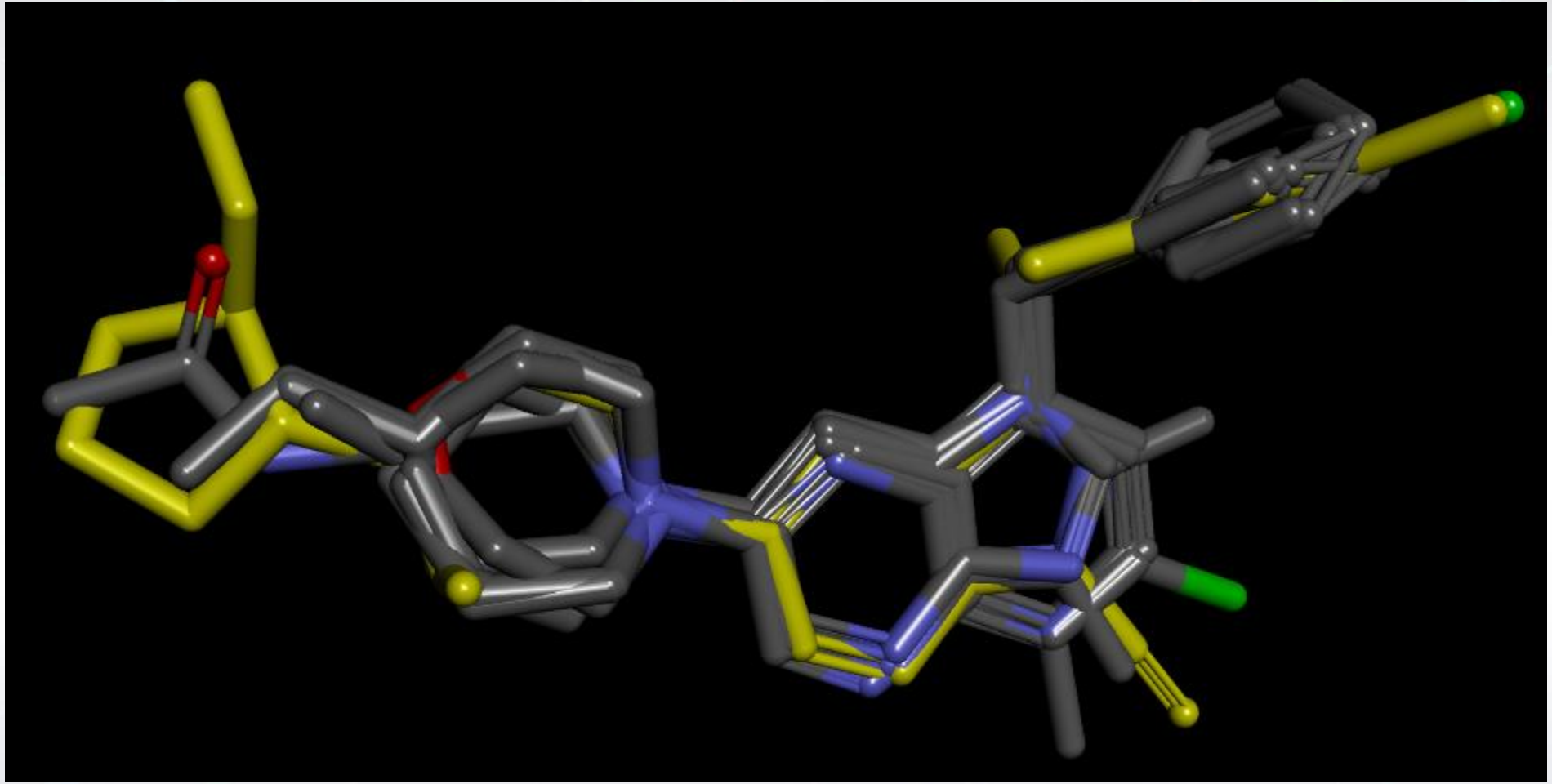
AIDD Results

108 molecules produced, all on the Pareto front



10 scaffolds, highlighted in blue, were produced

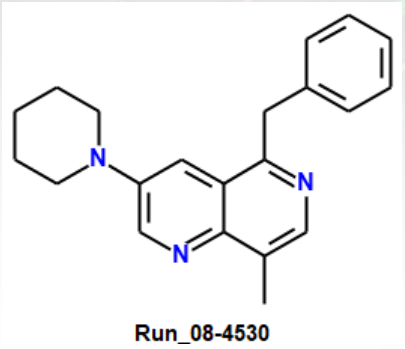
Overlay of AIDD Results on Reference



RAPT compound is colored yellow

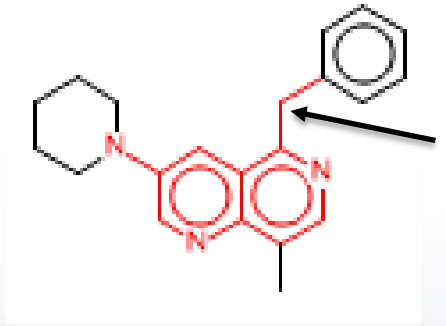
2nd Round of AIDD

- Use molecule from first run as seed molecule
- 1,6-naphthyridine scaffold
- Objectives
  - Synthetic difficulty
  - Fraction absorbed
  - Tanimoto from shape matching algorithm
- Scaffold query
  - c1([C,O,N,S;!R][a])n[cH]cc2n[cH]c(!@[A;R])[cH]c21
- Druglike filter
  - Limit to 3 Cl, Br, or I (SLQ [Cl,Br,I].[Cl,Br,I].[Cl,Br,I] > 1)
  - Limit to 3 aromatic rings (NPQ ArRing > 3)
  - Limit to 3 CL atoms (SLQ Cl >= 4)
  - Can't match RAPT molecule
- 10 generations
- 500 candidates per generation
- 1000 initial population



Run_08-4530

Alkyl ring



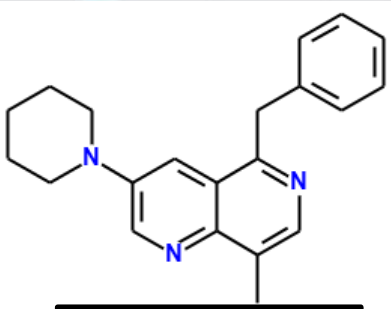
C, N, O, S (not ring)

Match from scaffold query

2nd AIDD Run of One Scaffold

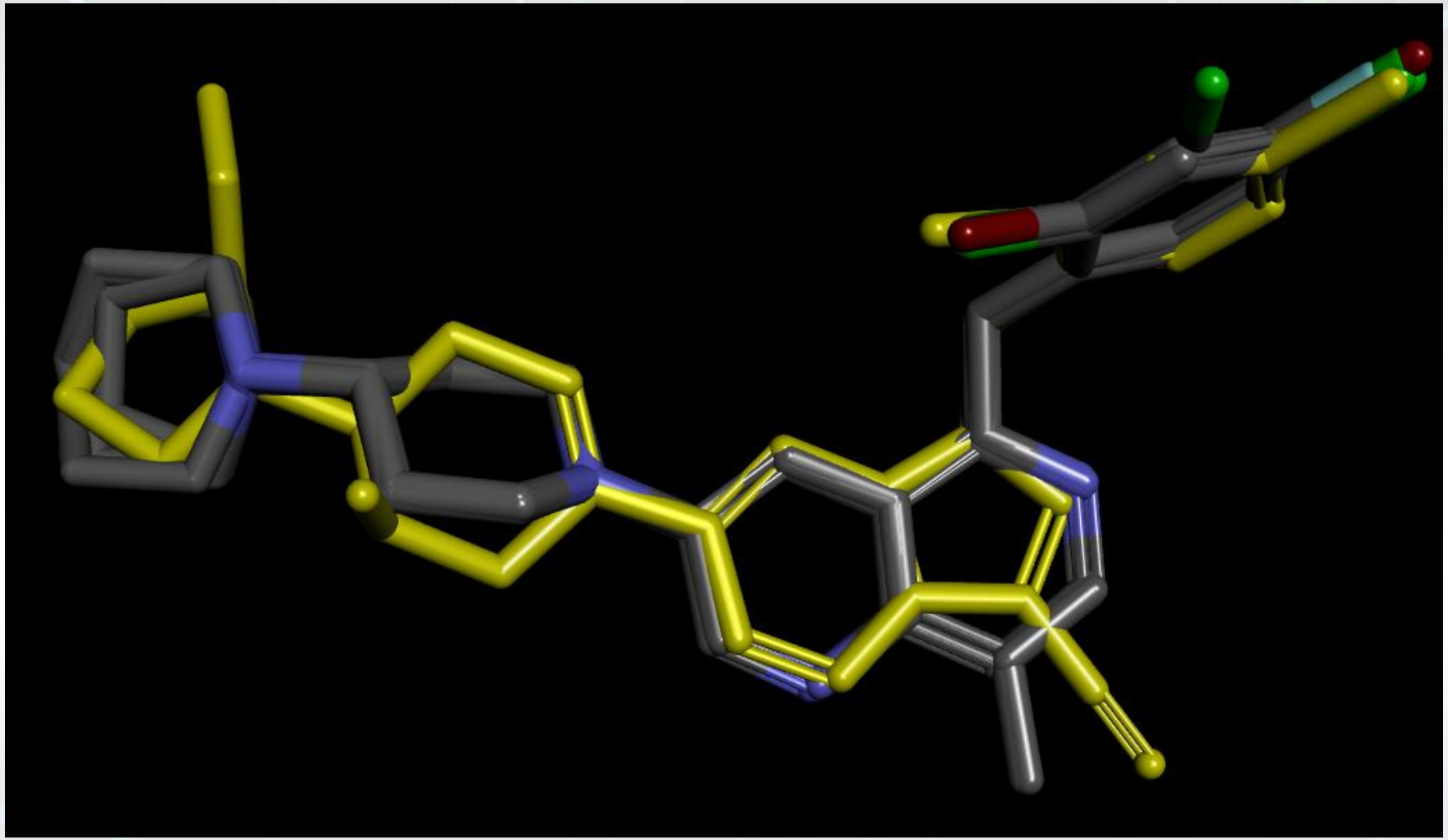
2952 0.732	5262 0.730	2987 0.730
2956 0.730	3984 0.729	3735 0.729
3769 0.728	3615 0.728	4255 0.727
1732 0.726		

10 best scoring ligands



Seed molecule

2nd AIDD Run of One Scaffold



RAPT compound is colored yellow

References

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Miah AH, Abas H, Begg M, Marsh BJ, O'Flynn DE, Ford AJ, Percy JM, Procopiou PA, Richards SA, Rumley SA. (2014) Lead identification of benzimidazolone and azabenzimidazolone arylsulfonamides as CC-chemokine receptor 4 (CCR4) antagonists. *Bioorg. Med. Chem.* 22, 4298-4311.

RAPT Therapeutics RPT193 https://rapt.com/pipeline/rpt193/.

RAPT Therapeutics FLX475 https://rapt.com/pipeline/flx475/.

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Cheminformatics Team

Rafal Bachorz

Pankaj Daga

Robert Fraczkiewicz

Eric Jamois

Jeremy Jones

Aleksandra Mikosz

David Miller

Dechuan Zhuang

Thanks for watching!

Michael Lawless
Senior Principal Scientist
michael.lawless@simulations-plus.com